Perceptual learning leads to long lasting visual improvement in patients with macular degeneration

Marcello Maniglia[1,2*], Andrea Pavan[3], Giovanni Sato[4], Giulio Contemori[5], Sonia Montemurro[5], Clara Casco[5]

[1] Université de Toulouse-UPS, Centre de Recherche Cerveau et Cognition, Toulouse, France

[2] Centre National de la Recherche Scientifique, Toulouse Cedex, France

[3]University of Lincoln, School of Psychology, Brayford Pool, Lincoln LN6 7TS, United Kingdom

[4]Centro di Riabilitazione Visiva Ipovedenti c/o Istituto L. Configliachi – Via Sette Martiri, 33, 35143, Padova, Italy

[5]University of Padova, Department of General Psychology, Via Venezia 8, 35131, Padova, Italy

***Corresponding author**

Marcello Maniglia

Centre de Recherche Cerveau & Cognition - UMR5549

Toulouse, France

Tel: +33 05-62-74-61-39

Email: maniglia@cerco.ups-tlse.fr

Abstract

Purpose: The study investigated whether perceptual learning (PL) of a task consisting in detecting a low contrast Gabor patch flanked above and below by high contrast Gabor patches presented monocularly in the preferred retinal locus (PRL) of patients with macular degeneration (MD), improved their residual visual functions.

Method: We measured contrast detection thresholds using both a Yes/No task (three MD patients and three controls) and a temporal two-alternative forced-choice task (2AFC; four MD patients and three controls).

Results: Both tasks produced a significant improvement in contrast sensitivity for the trained target. However, only in the case of the temporal-2AFC this improvement depended on the target-to-flankers distance. Furthermore, in both tasks PL improved visual acuity but with the temporal-2AFC task we found a higher degree of generalization of the training to untrained stimuli and tasks. In fact, we found a reduction of the crowding effect and an improvement of the contrast sensitivity for untrained spatial frequencies.

Although PL is more effective with a temporal-2AFC task, it is also present with a Yes/No task, suggesting that PL reflects sensory enhancement, rather than improvement in decision mechanisms. Most importantly, follow-up tests on MD patients showed that PL effects were retained between four and eight months, suggesting PL induced long-term neural plasticity in the visual cortex.

Conclusion: The results show for the first time that PL with a collinear configuration has strong, non-invasive and long lasting rehabilitative potential to improve vision in the PRL of patients with central vision loss.

Introduction

Macular degeneration (MD) is the leading cause of visual impairment in Western developed countries (Liu, Chan, & Tuo, 2012). This condition involves loss of central vision, including loss of contrast sensitivity and visual acuity, mostly caused by a foveal scotoma. Deprived of central vision, patients affected by MD usually adopt a region close to the scotomatous retina (the preferred retinal locus; PRL) as a new fixation spot (Timberlake, Peli, Essock, & Augliere, 1987; Guez, Le Gargasson, Rigaudiere, & O'Regan, 1993). The improvement of the quality of vision in this eccentric region has important implications for the rehabilitation of MD visual functions.

Many studies (Polat, Ma-Naim, Belkin, & Sagi, 2004; Polat, 2009; Tan & Fong, 2008; Chung, 2011; Chung & Truong, 2013) show that visual abilities such as visual acuity (VA) and the contrast sensitivity function (CSF) can be improved by training observers for several weeks in a Perceptual Learning (PL) task. One of the most efficient approaches consists in a contrast detection task for a low contrast Gabor patch flanked above and below by high contrast Gabor patches (Polat et al., 2004; Polat, 2009; Maniglia, Pavan, Cuturi, Campana, Sato, & Casco, 2011; Casco, Guzzon, Moise, Vecchies, Testa, & Pavan, 2014). For foveal stimuli, it has been found that collinear flankers placed at a distance of 3-4 times the wavelength of the target Gabor's carrier (λ) enhance target detection (Polat & Sagi, 1993, 1994a, 1994b), thus producing facilitation (i.e., lower contrast detection thresholds). On the other hand, for shorter target-to-flankers distances (i.e., 1–2λ), the target contrast detection threshold is increased compared to the condition in which the target is presented alone, thus resulting in suppression (i.e., higher contrast detection thresholds) (Polat & Sagi, 1993; Zenger & Sagi, 1996).

PL with collinear configuration increases facilitation, reduces suppression (Polat & Sagi, 1994b) and transfers to untrained, higher-level visual abilities such as VA and CSF (see Polat, 2009 for a review). In addition, there is recent psychophysical evidence of collinear facilitation in the near periphery of the visual field (4° of eccentricity), at a target-to-flankers distance larger than in the fovea (between 7λ and 8λ) (Maniglia et al., 2011; Maniglia, Pavan, & Trotter, 2015), suggesting that the spatial range of facilitatory lateral interactions is increased in the near periphery. Moreover, peripheral collinear suppression appears to be modulated by PL. Specifically, PL reduces suppression but does not increase facilitation (Maniglia et al., 2011). The PL effect with eccentric presentation transfers to untrained higher spatial frequencies and reduces the crowding effect (i.e., the inability of discriminating objects or letters in clutter; Levi, 2008; Pelli & Tillman, 2008). Consequently, PL might be considered a non-invasive and inexpensive behavioural rehabilitative technique to improve vision in the PRL of patients with central vision loss.

Few recent studies used PL with age-related macular degeneration (AMD) patients in order to improve their visual abilities (Chung, 2011; Rosengarth, Keck, Brandl-Rühle, Frolo, Hufendiek, Greenlee, & Plank, 2013; Plank, Rosengarth, Schmalhofer, Goldhacker, Brandl-Rühle, & Greenlee, 2014). For example, Rosengarth et al. (2013) trained a group of eight AMD patients with an oculomotor training and found improvements in reading speed and fixation stability between pre-tests and mid-tests, but not between pre-tests and post-tests. Moreover, no significant changes in BOLD signals were observed between pre and post training tests in early visual areas (V1, V2 and V3) or in associative areas (LOC, fusiform gyrus, ITG). Similarly, Plank et al. (2014) trained eight AMD patients to perform a texture-discrimination task at their PRL used for fixation. After six training sessions over three weeks, patients showed some small improvements in Vernier acuity for an eccentric line-bisection task, a weak positive correlation between the development of BOLD signals in early visual cortex and initial fixation stability, and a weak positive correlation between the increase in task performance and fixation stability. These improvements were accompanied by a modest alteration in the BOLD response in early visual cortex.

We argue that the small or short lasting improvements observed in these previous studies might depend on the training task used. In the present study MD patients and controls were trained in a contrast detection task using a collinear configuration. This procedure has been shown to probe neural plasticity (Polat & Sagi, 1994b) and producing significant generalization to other visual abilities not previously trained (e.g., VA, CFS, crowding), both in fovea and in the near periphery of the visual field (Polat et al., 2004; Tan & Fong, 2008; Polat, 2009; Maniglia et al., 2011; Casco et al., 2014). In particular, the aim of the present study was to investigate whether training contrast detection of a low-contrast target flanked by collinear high contrast flankers can improve untrained high-level visual abilities in MD patients. Seven MD patients were trained. Three MD patients performed a Yes/No task, and four performed a temporal two-alternative forced-choice task (temporal-2AFC). There is psychophysical evidence that a temporal-2AFC procedure is more effective in controlling response bias and criterion shift than a Yes/No task (Green & Swets, 1974). Furthermore, one relevant difference that we introduced between the Yes/No task and the temporal-2AFC was that only during the temporal-2AFC task an auditory feedback for incorrect responses was provided. Whereas in both tasks learning may improve sensory signals and modulate lateral interactions, feedback in the temporal-2AFC task may reinforce learning by maximizing decision mechanism through reward (Petrov, Dosher, & Lu, 2005; Lu & Dosher, 2010; Kumano & Uka, 2013).

In the present study we assessed the degree of generalization to different stimuli and tasks following perceptual training with a Yes/No task and a temporal-2AFC task. We hypothesized that being a temaporal-2AFC in combination with an auditory feedback a more robust procedure (Polat & Sagi, 2007), it should produce more generalization of the training to different stimuli and tasks.

Participants performed before and after PL different tasks including VA, CSF and crowding, both in their PRL and in a symmetrical, peripheral retinal position with respect to the PRL (i.e., Non-PRL). In addition, for three patients follow-up data were collected 4-8 months after the training.

In the case of the temporal-2AFC task, subjects also performed a transfer condition in which they had to detect a central vertical Gabor patch flanked by orthogonally oriented Gabor patches; in this case target's detection is not modulated by lateral interactions (Polat & Sagi, 1993; Polat & Norcia, 1996). This was done to verify that PL does not transfer to different flankers orientations, thus concluding that PL modulates specifically lateral interactions (Polat & Sagi, 1994b; Maniglia et al., 2011; Casco et al., 2014). Therefore, the training was not devised to specifically improve the target's detectability, but rather to probe the strengthening of neural connections that may lead to an improvement of untrained visual abilities (Polat et al., 2004; Polat, 2009). To date this is the first study using a perceptual training of collinear facilitation in order to produce long lasting improvements of visual functions in patients with central vision loss.

Experiment 1: PL with yes/no task

In Experiment 1 we investigated the effect of PL for collinear configurations using a single presentation interval with a Yes/No task (Amiaz, Zomet, & Polat, 2011; Polat & Sagi, 2007; Zomet, Amiaz, Grunhaus, & Polat, 2008). Other studies used a Yes/No task with eccentric stimuli and found collinear facilitation (Lev & Polat, 2011; Maniglia et al., 2011). We attempted to replicate these findings with MD patients since this task may be advantageous when compared to a temporal-2AFC task. In fact, the latter may be limited by the requirement to maintain fixation between the two temporal intervals (Lev & Polat, 2011). In independent blocks, stimuli were presented either on the PRL or the non-PRL. Fixation was maximally facilitated on the PRL since stimuli fell on this "special" region of the peripheral (intact) retina, spontaneously chosen for fixation. We asked whether stimulus presentation in the PRL produces better or different PL outcomes with respect to a stimulus presentation in the non-PRL.

Methods

Subjects

Three MD patients (MD1-MD3) and three normal-sighted subjects (C1-C3), performed a Yes/No contrast detection task of a vertically oriented Gabor patch (target) flanked above and below by two high contrast collinear Gabor patches (flankers). Patients' microperimetry is shown in Fig. 1 and observers' details are summarized in Table 1.

[FIG. 1 ABOUT HERE]

[TABLE 1 ABOUT HERE]

All participants gave their informed consent prior to their inclusion in the study. The study was performed in accordance with the ethical standards laid down by the Declaration of Helsinki (1964). The study was approved by the Ethics Committee of the Department of General Psychology, University of Padua (Protocol 1449). We obtained written informed consent from all participants involved in the study.

Apparatus and stimuli

PL stimuli

Participants sat in a dark room 57 cm from the screen. Stimuli were displayed on a 19-inch CTX CRT Trinitron monitor with a refresh rate of 75 Hz and a spatial resolution of 1024 x 768 pixels. Each pixel subtended 1.9 arcmin. The mean luminance of the display was 46.7 cd/m^2. Horizontal and vertical stimulus eccentricity for MD patients corresponded to their PRL in the lower left visual quadrant (5.0° x 4.2° for MD1, 4.5° x 3.2° for MD2 and 5.8° x 2.7° for MD3) or to the non-PRL in the upper left visual quadrant. In order to establish a reliable comparison, controls subjects were instructed to fixate centrally and the stimulus eccentricity was approximated to that of MD patients: 4° x 4° in either the lower left (corresponding to PRL) or upper left visual quadrant (non-PRL). Stimuli were generated with Matlab Psychtoolbox (Brainard, 1997; Pelli, 1997). We used a gamma-corrected lookup table (LUT) so that luminance was a linear function of the digital representation of the image.

Stimuli were Gabor patches consisting of a cosinusoidal carrier enveloped by a stationary Gaussian. Each Gabor patch was characterized by its sinusoidal wavelength (λ), phase (φ), and standard deviation of the luminance Gaussian envelope (σ) in the (x, y) space of the image:

$$G(x,y) = \cos\left(\frac{2\pi}{\lambda}x + \varphi\right)e^{\left(-\frac{x^2+y^2}{\sigma^2}\right)} \qquad \text{Eq.1}$$

with $\sigma = \lambda$ and $\varphi = 0$ (even symmetric). Gabors' spatial frequency was 2 and 3 cycles per degree (cpd) for MD patients and 3 cpd for controls. A vertical Gabor target (Fig. 2) was presented flanked, above and below, by two high-contrast Gabor patches (0.6 Michelson contrast).

[FIG. 2 ABOUT HERE]

Transfer stimuli

Peripheral visual acuity and crowding stimuli

Eccentric visual acuity (eccentric VA) and crowding effect were measured before and after PL sessions. Stimuli were generated using E-Prime software and presented at 57 cm from the same screen used for the perceptual training. The stimuli were 10 letters (D, N, S, C, K, R, Z, H, O, V) randomly presented for 133 ms. In the eccentric VA test, the target letter was presented in separate bocks either in the PRL or non-PRL for MD patients, and at 4° eccentricity for controls. The size of the letters varied according to a 1-up/3-down staircase (Levitt, 1971). The step size was 1 font size corresponding to streak width of 0.19 arcmin. The character type was Arial, and the starting font size was 20 (streak width of 3.72 arcmin). Subjects had to report verbally the letter displayed and the experimenter registered the answer. The session terminated after either 100 trials or 18 reversals. The acuity threshold, expressed as the font size for 79% correct identifications, was estimated by averaging the font size corresponding to the last 8 reversals.

For crowding two different letters flanked horizontally the target. The triplets were presented in separate bocks in the PRL and non-PRL for MD patients and at 4° eccentricity for controls. The MD patients were able to detect all the three letters at the largest spacing used. The size of both the target and flanking letters was set 30% higher than the VA threshold. We measured the critical spacing, i.e., the inter-letter distance for which observers could discriminate the target (the central letter) with 79% accuracy. We used a 1-up/3-down staircase (Levitt, 1971). The session terminated either after 100 trials or 18 reversals. Threshold was estimated by averaging the spacing values corresponding to the last 8 reversals.

Peripheral CSF stimuli

We measured peripheral contrast sensitivity functions (CSF) before and after PL by using sinusoidal gratings generated by a VSG2/3 graphics processor (Cambridge Research System Ltd, Rochester, Kent, UK). Gratings were displayed on a 17-inch Philips Brilliance 107P CRT monitor with a refresh rate of 70 Hz and a spatial resolution of 1024 x 768 pixels. The stimuli were vertical gratings displayed on the whole screen area (26 x 20 deg) with a central black circular window of the size of the patients' scotoma (diameter: ~8 deg). Contrast thresholds were estimated with the method of Limits for three spatial frequencies: 1, 2 and 4.5 cpd.

Procedure

Pre- and post-training evaluation

Participants performed a monocular eccentric-VA, crowding and CSF. All of these tests were repeated after the training sessions.

PL procedure

We used the psychophysical method of constant stimuli (MCS) and a Yes/No task in which the observers had to report whether the target was present or absent. The Yes/No task was performed with a vertical collinear configuration and target-to-flankers distances of 3λ, 4λ and 6λ presented in the left lower (PRL) and upper (non-PRL) visual quadrants. Stimuli were presented for 133 ms. A daily session consisted of 12 experimental blocks. Each experimental block lasted approximately 5 minutes and consisted of 48 randomly presented trials that corresponded to 8 repetitions of 6 contrast levels (Michelson contrast): two values above and two values below (in steps of 0.1 log units) the contrast threshold estimated before the training and individually for each observer. Contrast thresholds were estimated using a temporal-2AFC task and a 1-up/3-down staircase (Levitt, 1971), leading to a 79% correct detection. In addition, we also used a contrast value of zero for catch trials.

We trained two spatial frequencies (2 and 3 cpd), three target-to-flanker distances (2λ, 3λ and 6λ) and two retinal position (PRL and non-PRL). A standard daily session consisted of 576 trials separated in 12 blocks, in which the target-to-flankers distance was varied starting from the largest distance (6λ), and the spatial frequency was varied starting from the lowest value (2 cpd). In the first six blocks stimuli were presented in the PRL location, whereas in the last six blocks stimuli were presented in the non-PRL position. This training regime was performed 3 times a week. Thus, each participant performed 24 sessions distributed over the course of 8 weeks. For each participant, and for each combination of spatial frequency, target-to-flankers distance and stimulus location, we obtained the probability of correct detection associated to each of the six contrast levels. *d'* were derived by the probability of responding "yes I see the target" when it was absent (i.e., False Alarm) and the probability of responding "yes" when the target's contrast was equal to the second highest contrast value presented (corresponding approximately to the 90% of observers' contrast threshold).

PL Results

The effect of PL on sensitivity (d')

PL results (pooled for retinal location) are shown in Figures 3. Overall, the results show that PL increases *d'*.

A mixed ANOVA including as factors the Group (patients vs. controls), PL (pre- vs. post-training) and the Target-to-flankers distance reported a significant main effect of PL ($F_{1,4} = 28.07$, $p = 0.006$, $partial\text{-}\eta^2 = 0.88$), while the effect of Group only approached significance ($F_{1,4}$=7.37, p=0.053, $partial\text{-}\eta^2$ =0.65). The effect of Target-to-flankers distance was not significant ($F_{2,8}$=3.29, p=0.091, $partial\text{-}\eta^2$ =0.45). Moreover, we did not find any significant interaction. These results indicate that PL generally increased contrast sensitivity for the flanked target. Taken together, the results of PL on *d'* indicate that PL render subjects more sensitive to contrast variations in all conditions.

[FIG. 3 ABOUT HERE]

The effect of PL on retinal location

Fig. 4 shows the effect of PL averaged across the spatial frequencies and target-to-flankers distances. The PL effect does not differ in the two fixation conditions (PRL and non-PRL), suggesting that MD patients can maximize the effect of PL even if the stimulus location is not optimal for fixation (Casco, Campana, Grieco, Musetti, & Perrone, 2003).

[FIG. 4 ABOUT HERE]

Transfer to Peripheral CSF

Fig. 5 shows the contrast sensitivity function (CSF) for MD patients and controls. We found an appreciable although non consistent improvement in contrast sensitivity for the trained spatial frequency (i.e., 2 cpd), but only MD3 showed improvement to untrained spatial frequencies of 1 and 4.5 cpd.

[FIG. 5 ABOUT HERE]

Transfer to Peripheral visual acuity and crowding

Eccentric vision has higher optical blur and lower spatial resolution with respect to central vision (for a review see Strasburger, Rentschler & Juttner, 2011). Therefore, it is important to establish whether PL of collinear configurations transfers to the letter recognition task (eccentric VA), this is because there is a relationships between contrast detection and letter recognition

(Chung, Legge, & Tjan, 2002; Chung, Mansfield, & Legge, 1998; Legge, Rubin, Pelli, & Schleske, 1985; Levi, Song, & Pelli, 2007; Majaj, Pelli, Kurshan, & Palomares, 2002; Patching & Jordan, 2005; Salomon & Pelli, 1994). Transfer of PL to eccentric VA is shown in Fig. 6, in which controls' data are pooled for retinal location and MD patients' data are shown separately for the two retinal locations. The improvement in eccentric VA was not consistent for all the controls, in agreement with our previous data (Maniglia et al., 2011). However, eccentric VA generally improved in the MD group.

[FIG. 6 ABOUT HERE]

Transfer of PL for crowding is shown in Fig. 7. Crowding was not reduced by PL in any of the MD patients. Instead, as we found in our previous study (Maniglia et al., 2011), PL generally reduced the crowding effect in normal sighted subjects.

[FIG. 7 ABOUT HERE]

In explaining the lack of the crowding effect for MD patients it should be noted that for MD2 and MD3 critical spacing was already very low before PL, confirming the evidence of a major use-dependent responsiveness of eccentric vision in MD patients (Casco et al., 2003; De Stefani, Pinello, Campana, Mazzarolo, Lo Giudice, & Casco, 2011) and an overall reduced crowding effect for the PRL location in MD patients without previous training (Chung, 2011).

Discussion of Yes/No task results

Results with the Yes/No task showed that PL increased contrast sensitivity for the flanked target in both MD and control groups. This improvement is associated to a more conservative criterion (i.e., less FA). We also found that the improvement in target detection was independent of target-to-flankers distance, while in our previous study (Maniglia et al., 2011) we did not find an effect of PL only at a target-to-flankers distance of 8λ.

The general improvement of contrast sensitivity at both retinal locations was unexpected. One possibility is that it reflects, in addition to or instead of a PL dependent improvement in contrast sensitivity, a PL increase of attentional resources to the target configuration. Indeed, in our previous study (Maniglia et al., 2011), the stimuli in each block were randomly presented in one of the two visual hemi-fields at 4° eccentricity. Therefore attention had to be distributed across the two positions instead of being focused to one single fixed position, i.e., either the PRL or the non-PRL. Reduced attentional demands may have produced a larger increase of d's in the present study with respect to that observed in our previous study (Maniglia et al., 2011) in the same stimulus conditions. To check for this possibility we tested whether the *d'*s ratio (i.e., *d'* after PL / *d'* before PL) obtained by MD and control subjects differed from the average ratio obtained by the eight subjects tested binocularly by Maniglia et al. (2011) in corresponding stimulus conditions (i.e., 3λ and 4λ for a spatial frequency of 2 cpd). The results of a Crawford t-test (Table 2) revealed a significant difference only for 3λ distance in patient MD3.

[TABLE 2 ABOUT HERE]

This suggests a little role of attention in producing the PL effect, which may rely on a flankers' induced modulation of contrast sensitivity.

Experiment 2: PL with a 2AFC task

Four different MD patients and three controls performed a contrast detection task with collinear configurations but using a temporal-2AFC task with feedback on incorrect trials. Temporal-2AFC procedure is considered to be effective in reducing response bias and criterion shift with respect to a Yes/No task (Green & Swets, 1974). Giorgi and colleagues (2004) showed that a temporal-2AFC task is a suitable procedure to measure collinear facilitation as a function of the target-to-flankers distance, and it is more effective than a spatial-2AFC. In addition, PL with a temporal-2AFC task combined with auditory feedback may reinforce learning by maximizing decision mechanism through reward (Kumano & Uka, 2013), which in turn may affect PL and transfer tasks differently from a Yes/No task without feedback.

On the other hand, temporal-2AFC may not be an adequate psychophysical procedure for several reasons. First, simulation studies showed that threshold estimation with a temporal-2AFC task are less efficient with respect to a Yes/No paradigm, using the same number of trials (Alcalà-Quintana & Garcìa Pèrez, 2004; Garcìa-Pèrez, 1998; Garcìa-Pèrez & Peli, 2001; Garcìa-Pèrez & Alcalà-Quintana, 2005; Kershaw, 1985; Taylor & Creelman, 1967). Second, when used with parafoveal stimuli, performance may be limited by the subjects' ability to maintain fixation between the first and the second interval (Lev & Polat, 2011), a problem that becomes insidious in MD patients that have peripheral and often unstable fixation.

In Experiment 2 we trained four different MD patients with a temporal-2AFC task. The aim was to assess whether using a different procedure produces a different PL effect and a different amount of transfer to stimuli and tasks not previously trained. In addition, before and after the perceptual training we measured contrast detection thresholds for a vertical target flanked by orthogonally oriented flankers (orthogonal configuration) and flanked by vertically oriented flankers (collinear configuration). Using the orthogonal configuration we could assess whether PL was specific for the trained collinear configuration, since lateral interactions are specific for collinearly-flanked targets (Polat & Sagi, 1994b).

Method

Subjects

Four MD patients (MD4-MD7) and three controls (C4-C6) participated. Patients' microperimetry is shown in Fig. 8 and observers' details are summarized in Table 3.

[FIGURE 8 ABOUT HERE]

[TABLE 3 ABOUT HERE]

PL Stimuli

Apparatus and stimuli were the same as used for the Yes/No task. Gabor patches had a spatial frequency of 2 and 3 cpd for controls. For MD4 Gabor patches had a spatial frequency of 1 and 3 cpd, for MD5 spatial frequencies were 4, 5 and 6 cpd, for MD6 we used a spatial frequency of 3 cpd and for MD7 the spatial frequency was 2 cpd. Two high contrast (0.6) collinear flankers were placed at various distances above and below the target (i.e., 2λ, 3λ, 4λ, and 8λ). The tests were conducted monocularly, either in the left eye (MD4 and MD6), or the in the right eye (MD5 and MD7). Patients MD5 was trained with both vertical and horizontal collinear configurations since for neither configurations the flankers fell in the scotomatous area.

Transfer Stimuli

To assess whether training transferred to viewing conditions similar to those of everyday life, transfer stimuli were presented centrally (except for crowding) and observers were asked to use optimal fixation. We did not collect transfer data for controls since their central vision is unimpaired.

Visual acuity and crowding stimuli

We used the FrACT (Freiburg Visual Acuity and Contrast Test) Software (Bach, 1996). Observers viewed the stimulus monocularly for a maximum of 30 s with Landolt-C with four gap orientations. Observers had to discriminate the orientation of the gap (4AFC). Stimulus and gap sizes were varied according to the accuracy of the response.

Crowding was measured only for MD patients as reported for the Yes/No task, i.e., with stimuli presented in the PRL.

CSF stimuli

CSF was measured using FrACT Software only for MD patients. Stimuli were Gabor patches of 5 deg (full width at half maximum) with four different orientations (horizontal, vertical, diagonal at 45° and 135°). Observers performed monocularly an orientation discrimination task (4AFC). Stimulus disappeared immediately after the observers' response. Stimuli were displayed for a maximum of 30 s. The contrast of the stimulus was varied according to a BEST PEST procedure. The viewing distance was 200 cm and an acoustic feedback was provided for incorrect trials. Spatial frequencies tested were 1, 3, 5, 7, 9 and 11 cpd.

Orthogonal configuration

After the training observers also performed, with the same presentation conditions used for the PL stimuli, a transfer condition in which they had to detect a central vertical target flanked by orthogonally oriented Gabor patches. In addition, patient MD5, who was trained with horizontal collinear configurations, after the training performed the contrast detection task on a horizontal stimulus configuration with a horizontal target flanked by vertically oriented Gabor patches.

Procedure

Pre- and post-training evaluation

Before PL, we measured monocularly VA, crowding, CSF and the target contrast thresholds for orthogonal configuration. All the tests were repeated after the training sessions.

PL procedure

The contrast threshold of the target was varied according to 1up/3down staircase (Levitt, 1971). Participants performed a temporal-2AFC. The target was presented in one of the two temporal intervals whereas the flankers were always presented in both temporal intervals. Observers had to report in which temporal interval the target was presented. A feedback was provided for incorrect trials. Each block terminated after 120 trials or 16 reversals. Contrast thresholds were estimated by averaging the contrast values corresponding to the last 8 reversals.

The amount of collinear facilitation was estimated by computing the threshold elevation (*TE*) as:

$$TE = \log_{10}\left(\frac{CT\_Collinear}{CT\_Orthogonal}\right) \qquad \text{Eq. 2}$$

Where *CT_Collinear* is the contrast threshold estimated in the collinear condition, whereas *CT_Orthogonal* is the contrast threshold estimated in the orthogonal condition. *TE* was calculated separately for each target-to-flankers distance (i.e., 2λ, 3λ, 4λ, and 8λ). During the training, the target-to-flankers distance was varied within a daily session, starting always with the largest distance, whereas the global orientation of the stimulus configuration (horizontal and vertical) was repeated twice across four daily sessions. Stimulus duration was 250 ms for MD4, MD6 and MD7, whereas for MD5 and controls it was 133 ms. There were 6-8 weekly PL sessions for each spatial frequency, starting from the lowest. Patients performed the training in their PRL.

Results

PL results

Results for PL are shown in Fig. 9. We did not perform a statistical analysis of the PL effect, given that subjects did not perform the PL task under the same conditions in terms of spatial frequency and stimulus duration. Overall, PL substantially reduced the contrast thresholds and follow-up data (available for MD6 and MD7) show that the improvement was retained between four to eight months. For controls the reduction only occurred at a target-to-flankers distance of 2λ. However, we cannot exclude an effect of PL for the other distances since contrast threshold were measured by using stimuli generated with 8-bit luminance resolution.

[FIGURE 9 ABOUT HERE]

Modulation of lateral Interactions by PL

TE values are reported in Fig. 10. For MD patients (except MD7) *TE* shows collinear facilitation after PL (i.e., negative values) at target-to-flankers distances of 3, 4 and 8λ (Polat & Sagi, 1993; Maniglia et al., 2011; Casco et al., 2014). For controls instead, the effect of PL mainly consisted in a reduced suppression at 2λ.

[FIGURE 10 ABOUT HERE]

Overall, *TE* is modulated by PL. In controls PL decreases suppression at 2λ. These results suggest a different pattern of lateral interactions in MD patients and controls which are both modulated by PL.

Transfer to VA

Fig. 11 shows visual acuity thresholds for discriminating the gap orientation in the Landolt-C test, obtained before and after PL for MD patients. Follow-up data collected between four and eight months after the training are also reported for patients MD5-MD7.

[FIGURE 11 ABOUT HERE]

Results show an improvement of 0.5 logMAR for MD4, 0.3 logMAR for MD5, 0.2 logMAR for MD6 and 0.15 logMAR for MD7. Follow-up data (only available for three MD patients [MD5-MD7]) show partial or complete maintenance of the PL effect after 4-8 months.

Transfer of PL to crowding

The transfer of PL to crowding is shown in Fig. 12. Critical spacing is decreased after PL in three MD patients and this transfer is retained by MD5 after eight months.

[FIGURE 12 ABOUT HERE]

Transfer to CSF

Fig. 13 shows the contrast sensitivity functions for MD patients. PL improved contrast sensitivity for untrained spatial frequencies (5 and 7 cpd for MD4; 7, 9 and 11 cpd for MD5; 5, 7, 9 and 11 cpd for MD6; 5 cpd for MD7). Moreover, follow-up data indicated that the transfer was retained, but only for patients MD5 and MD7.

[FIGURE 13 ABOUT HERE]

Discussion of temporal-2AFC results

In Experiment 2 MD patients and controls were trained using a temporal-2AFC task. For controls, PL mainly reduced suppression by the flankers at the lowest target-to-flankers distance (i.e., 2λ), consistently with previous studies on PL and collinear facilitation in the near periphery of the visual field (Maniglia et al., 2011). Moreover, PL in patients MD4, MD5 and MD6 generally increased collinear facilitation. Most importantly in MD patients, as with the Yes/No task, PL transferred to untrained visual tasks, confirming that PL generalizes to untrained higher level visual functions such as the CSF, VA and reduces the crowding effect. Overall, these results suggest that a temporal-2AFC task is appropriate to induce modulation of lateral interactions by PL and transfer of PL to untrained high level functions in MD patients.

General discussion

The effect of PL in detecting a target when flanked by high contrast collinear flankers was assessed with a Yes/No task (Experiment 1) and a temporal-2AFC task (Experiment 2) for two distinct groups of patients with macular degeneration (MD).

In the Yes/No task the results of PL on *d'*s indicate that PL increases sensitivity at all target-to-flanker distances in both groups. With the temporal-2AFC task, the reduction of contrast threshold is associated, for three MD subject (MD5, MD6 and MD7), to a PL-dependent increase in facilitatory lateral interactions and, for controls, to a reduction of inhibitory lateral interactions.

The transfer results indicate that PL with a low-level visual task yields significant perceptual benefits to untrained visual functions. Either PL procedures (i.e., Yes/No and temporal-2AFC) improve visual acuity, whereas PL with a temporal-2AFC task transfer to CSF and reduces the crowding effect (for similar results see Polat, 2009; Polat et al., 2004; Tan & Fong, 2008; Maniglia et al., 2011; Casco et al., 2014).

The PL-dependent modulation of lateral interactions with the temporal-2AFC task suggests more directly a refinement of lateral interactions between target and flankers by PL. This confirms the results of Giorgi et al. (2004) that a temporal-2AFC task is a suitable procedure to measure collinear facilitation.

The transfer of PL is relevant for clinical purposes and it also raises the question of the locus of PL (Polat, 2009; Sagi, 2011). Our transfer results suggest that PL of a low-level visual task modulates visual processes at different levels of complexity, depending on the PL task.

Visual acuity was improved by both PL procedures (i.e., Yes/No and temporal-2AFC). This improvement may be related to the improvement in contrast sensitivity found in both tasks.

In, addition, we found that PL with a temporal-2AFC task transferred to untrained stimuli (i.e., untrained spatial frequencies and crowded letters) and tasks (i.e., letter identification and orientation discrimination). Instead PL with Yes/No task did not show the same degree of transfer. The positive results we found especially in the case of the temporal-2AFC, certainly depends on the training of lateral interactions, known to probe neural plasticity (Polat & Sagi, 1994b). In particular, this dependency holds for the transfer on the crowding effect, which may be related to the modulation of lateral interactions by PL, specifically found with the temporal-2AFC task. We have previously suggested (Maniglia et al., 2011; Casco et al., 2014) that the modulation of lateral interactions by PL may reduce crowding. To this purpose Pelli and colleagues (2004) argued that crowding depends on an excessive features integration process, so it is possible that the modulation of lateral-interactions at low-level of visual processing may induce a more appropriate balance between inhibition and integration mechanisms at a higher level (Maniglia et al., 2011).

In addition to the effect of PL on lateral interactions, the PL effect we observed with a temporal-2AFC may be related to the addition of an auditory feedback during the task, thus maximizing in decision mechanisms the read-out of sensory signals through reward (Kumano & Uka, 2013; Petrov et al., 2005). Indeed there is psychophysical evidence that inner reward/feedback can improve performance (Gibson & Gibson, 1955; Herzog & Fahle, 1998; Petrov, Dosher, & Lu, 2006; Shibata, Yamagishi, Ishii, & Kawato, 2009; Sasaki, Nanez, & Watanabe, 2010). For example Shibata et al. (2009) found that also a "fake" feedback indicating a larger performance improvement facilitated learning compared with genuine feedback. In addition, the authors found that variance of the "fake" feedback also modulated learning, suggesting that feedback uncertainty can be internally evaluated biasing decision mechanisms. Therefore, it is interesting to speculate whether the auditory feedback during the training task may have reinforced the transfer of PL. This possibility is interesting because maximizing the read-out of channels selective for different spatial frequencies and orientation may explain why PL with a temporal-2AFC task transferred to untrained spatial frequencies and untrained task (e.g., the orientation discrimination task, instead of a detection task, we used when measuring the CSF).

In conclusion, the present study provides new insights on the use PL to improve residual visual functions in the periphery of the visual field of AMD patients.

Previous studies (Chung, 2011; Rosengarth et al., 2013; Plank et al., 2014) aimed at improving a specific visual ability (e.g., texture discrimination, fixation stability) by directly training it. In these studies, authors used perceptual tasks (guided saccades, texture discrimination) known for their high specificity of learning, so generalization of learning to other visual abilities, triggered by changes in neural plasticity, was unlikely to happen. Consistently, Rosengarth et al. (2013) reported an increase in patients' performance only between pre- and mid-test measurements, but not between pre- and post-tests, showing that an oculomotor training might not be robust enough to produce long lasting changes. Moreover, functional neuroimaging data from both studies

(Rosengarth et al., 2013; Plank et al., 2014) showed no changes neither in the primary visual areas (V1, V2 and V3) nor in higher visual areas (e.g., LOC, fusiform gyrus, ITG).

In addressing the issue of whether PL can be used as a rehabilitative method for MD, one is faced with the problem of eye movements control in MD patients. Our patients had one single and localized PRL but we found no difference between PRL and non-PRL presentation. This aspect should be taken into account when planning a training protocol for MD patients who often have non-localized PRL or more than one PRL (Timberlake et al., 1987). However, since it is unpractical to use eye movements recording during PL, it should be considered whether it is more appropriate to present randomly the stimuli either in the right or in the left visual hemi-field for very short durations, a procedure that reduces eye movements (Casco et al., 2003) or simply train the PRL.

In conclusion, in this study we proved for the first time that training lateral interactions is efficacious in improving the residual visual functions in the periphery of the visual field of MD patients. Moreover, these improvements seem to be long lasting; a follow-up conducted between four and eight months showed good retention of the PL and transfer effects. Consequently, the perceptual training scheme presented represents a concrete possibility for a non-invasive rehabilitative visual training regime for patients suffering of central vision loss.

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TABLE AND FIGURE CAPTIONS

Table 1. Details of the MD patients and control participants that performed the Yes/No task. Details include: type of deficit, gender, age, size of the scotoma (deg), position of the PRL (deg), tested eye and visual acuity (VA).

Table 2. The results of a Crawford t-test between the *d'*s ratio for MD and control subjects (i.e., *d'*s after PL / *d'*s before PL) and the average *d'* ratio calculated on the data of Maniglia et al. (2011) across eight subjects tested binocularly and in comparable experimental conditions (i.e., 3λ and 4λ for a spatial frequency of 2 cpd).

Table 3. Details of the MD patients and controls that performed the temporal-2AFC task. Details include: Type of deficit, gender, age, size of the scotoma (deg), position of the PRL (deg), tested eye and visual acuity (VA).

Fig. 1. Nidek PM1 microperimetry of the left eye of MD1 (left panel), of the left eye of MD2 (central panel), and of the right eye of MD3 (right panel). The blue points represent the dispersion of monocular fixation pattern that indicates the location of PRL, i.e., the part of the retina that is used by the patients during fixation tasks.

Fig. 2. Stimulus configuration used in the learning sessions. Only one spatial frequency is shown (i.e., 3 cpd). A central target Gabor is flanked by two high-contrast Gabor patches of the same orientation and spatial frequency. Panels from left to right show the five target-to-flankers distances trained: 2λ, 3λ, 4λ, 6λ and 8λ.

Fig. 3. *d'* estimated before and after PL as a function of target-to-flankers distance for each participant of the MD group (top row) and control group (bottom row). *d'* are pooled for the two retinal locations (i.e., PRL and non-PRL).

Fig. 4. Mean *d'* obtained by MD patients before and after PL with stimuli presented either in the PRL or in the non-PRL. Data are averaged across the spatial frequencies and target-to-flankers distance employed. Error bars ±SEM.

Fig. 5. Contrast sensitivity as a function of the spatial frequencies of 1, 2 and 4.5 cpd is shown separately for each MD patient. Mean contrast sensitivity is reported for the control group. Error bars ±SEM.

Fig. 6. Eccentric visual acuity (arcmin) for MD patients, separately for the two retinal positions (i.e., PRL [left panel] and non-PRL [central panel]). Mean eccentric visual acuity (data are pooled across the two retinal locations) is also shown for the control group (right panel). Error bars ±SEM.

Fig. 7. Critical spacing (deg) for MD patients in the PRL (left panel) and non–PRL (central panel) retinal locations. Mean critical spacing is also shown for the control group (right panel) for which data are pooled across the two retinal locations. Error bars ±SEM.

Fig. 8. Nidek PM1 microperimetry of patients MD4 (Left eye), MD5 (Right eye), MD6 (Left eye) and MD7 (Right eye). The blue points indicate the part of the retina that is used by the patient during fixation tasks.

Fig. 9. Contrast thresholds as a function of the target-to-flankers distance are shown individually for MD patients. Mean contrast thresholds are shown for controls. Thresholds are averaged across the two global stimulus configuration (horizontal and vertical) and spatial frequencies trained: 1 and 3 cpd (MD4); 4, 5 and 6 cpd (MD5), 3 cpd (MD6) and 2 cpd (MD7). Follow-up data are also reported for MD6 and MD7. Contrast thresholds for the control subjects have been pooled across the spatial frequencies used (2 and 3 cpd). Error bars ±SEM.

Fig. 10. Threshold elevation (*TE*) values (i.e, lateral interaction curves) as a function of the target-to-flankers distance for four MD patients and controls. *TE* is averaged across the two global configurations (horizontal and vertical) and spatial frequencies trained: 1 and 3 cpd (MD4); 4, 5 and 6 cpd (MD5), 3 cpd (MD6), 2 cpd (MD7) and 2 and 3 cpd (controls). Follow-up data are also reported for MD6 and MD7. The dashed line represent the point of no modulation. Error bars ±SEM.

Fig. 11. Visual acuity (logMAR) estimated in the Landolt-C test for MD patients before and after PL. Grey bars represent follow-up for patients MD5-MD7 after 4-8 months.

Fig. 12. Critical spacing (deg) for MD patients before and after PL. Follow-up data are also reported for MD5, MD6 and MD7.

Fig. 13. Contrast sensitivity function (CSF) of MD patients measured for spatial frequencies ranging from 1 to 11 cpd.

TABLES

Patients	Deficit	Gender	Age	Scotoma size (diameter)	Position of PRL	Tested eye	(VA)
MD1	Stargardt	Female	38	11°	Left-down 5.0°-4.2°	LE	2/10
MD2	AMD	Female	64	6°	Left-down 4.5°-3.2°	LE	1/10
MD3	JMD	Male	32	5°	Left-down 5.8°-2.7°	RE	3/10
C1	none	Female	26	none	none	Non-dominant	10/10
C2	none	Female	28	none	none	Non-dominant	10/11
C3	none	Female	24	none	none	Non-dominant	10/12

Table 1.

	3λ		4λ	
Observer	***t***	***p***	***t***	***p***
MD1	1.25	0.25	-0.371	0.72
MD2	0.526	0.62	1.299	0.231
MD3	2.893	0.02*	0.408	0.69
C1	0.25	0.81	-0.668	0.52
C2	0.107	0.92	-0.334	0.75
C3	-0.012	0.99	-0.037	0.97

Table 2.

Patients	Deficit	Gender	Age	Scotoma size (diameter)	Position of PRL	Tested eye	(VA)
MD4	CRSC	Male	50	4°	Left-up 2.0°-1.0°	LE	2/10
MD5	Macular hole	Female	49	3°	Right-up 1.5°-1.0°	RE	7/10 (LAC)
MD6	Best disease	Male	58	8°	Left-up 4.0°-2.7°	LE	2/10
MD7	CRD	Male	62	6°	Left 4.5°	RE	2/10
C4	none	Female	54	none	none	Non-dominant	10/10
C5	none	Male	54	none	none	Non-dominant	10/10
C6	none	Male	64	none	none	Non-dominant	10/10

Table 3.

FIGURES

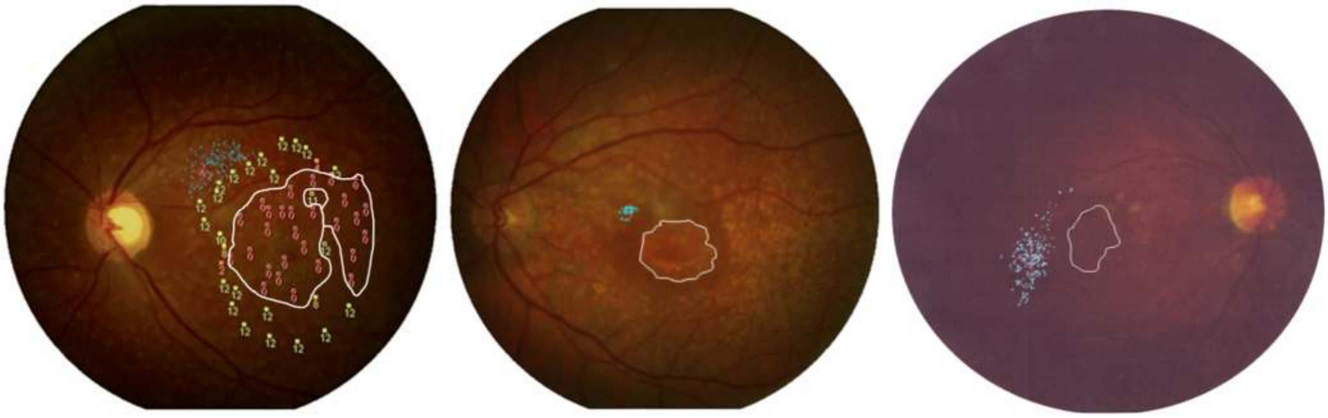


Fig. 1.

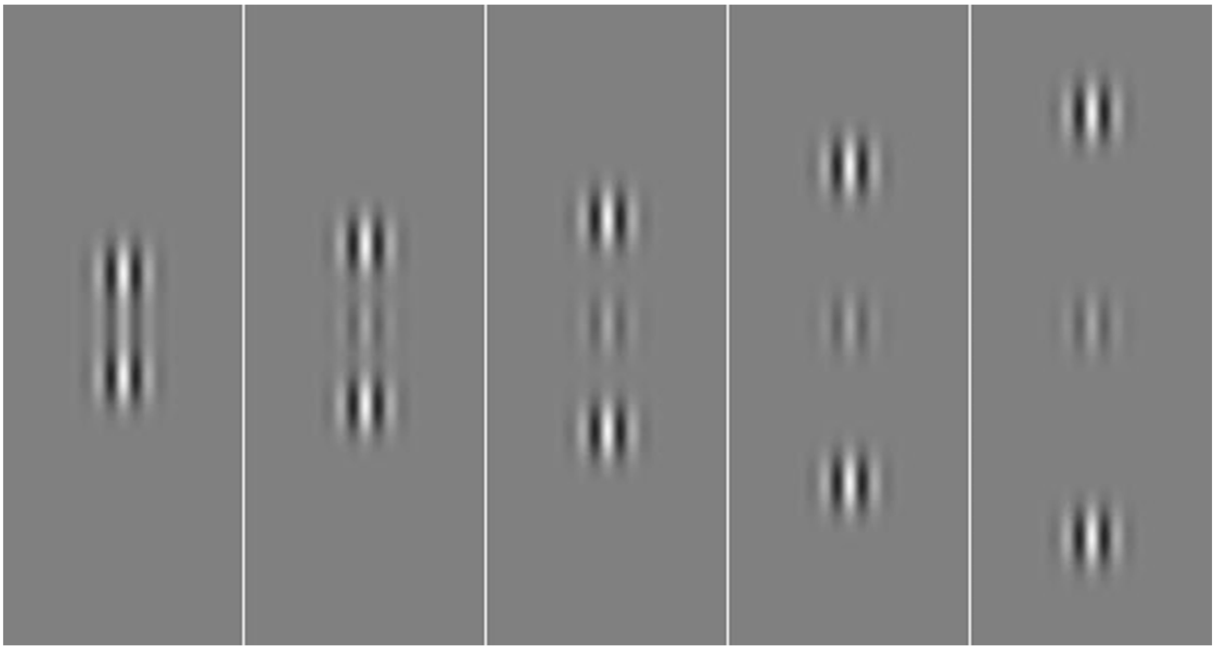
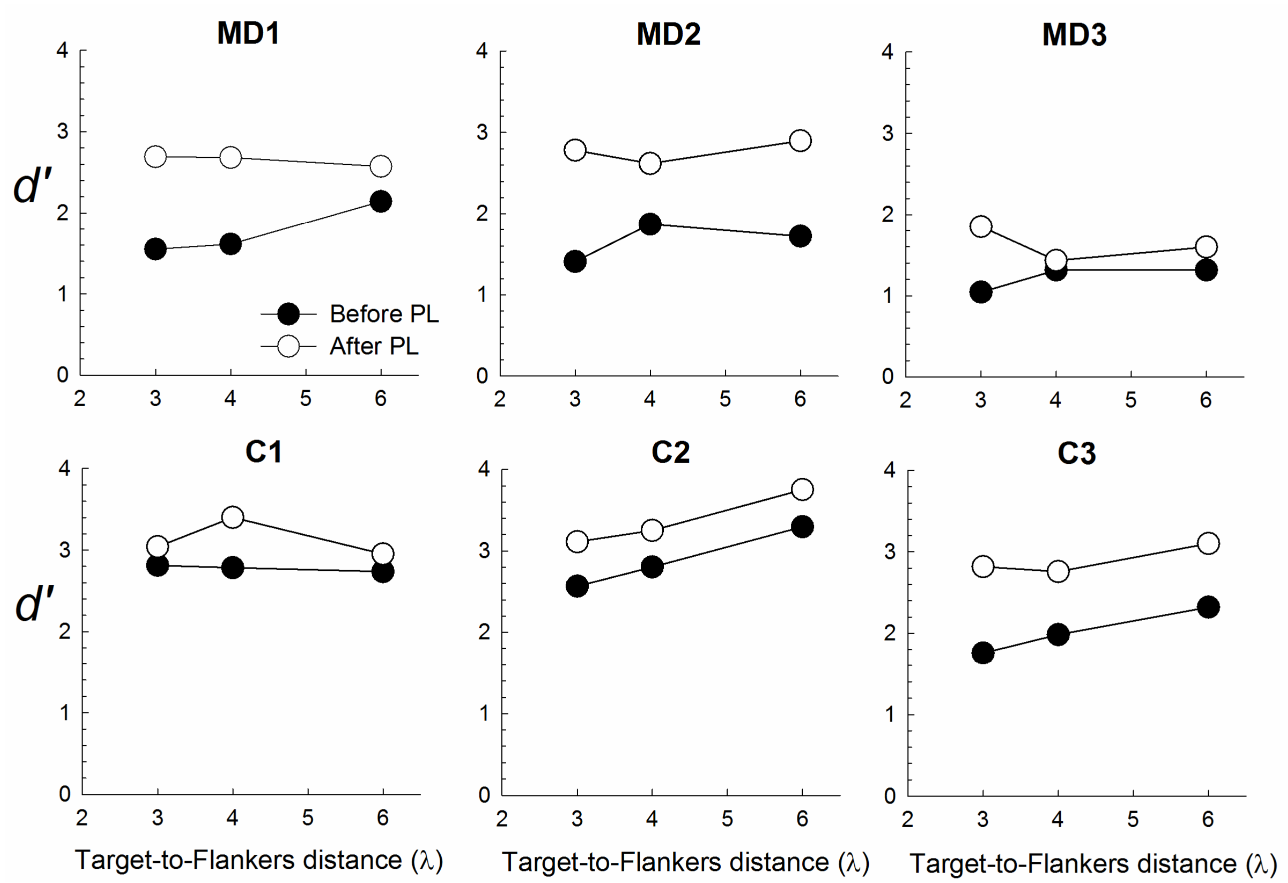


Fig. 2.



MD1
MD2
MD3
C1
C2
C3
d′
Before PL
After PL
Target-to-Flankers distance (λ)

Fig. 3.

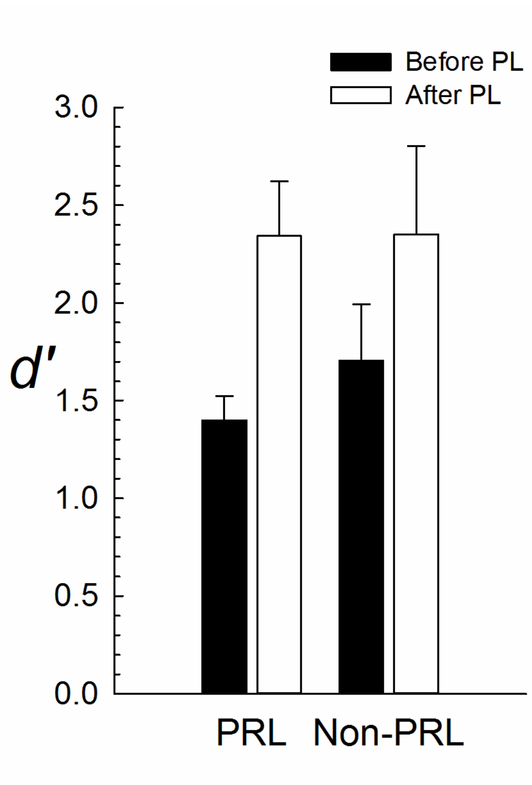


Fig. 4.

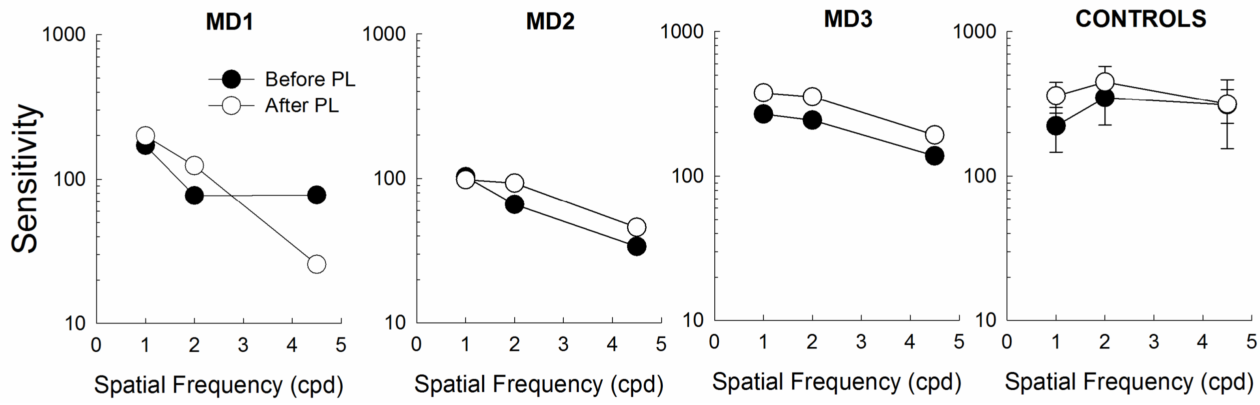
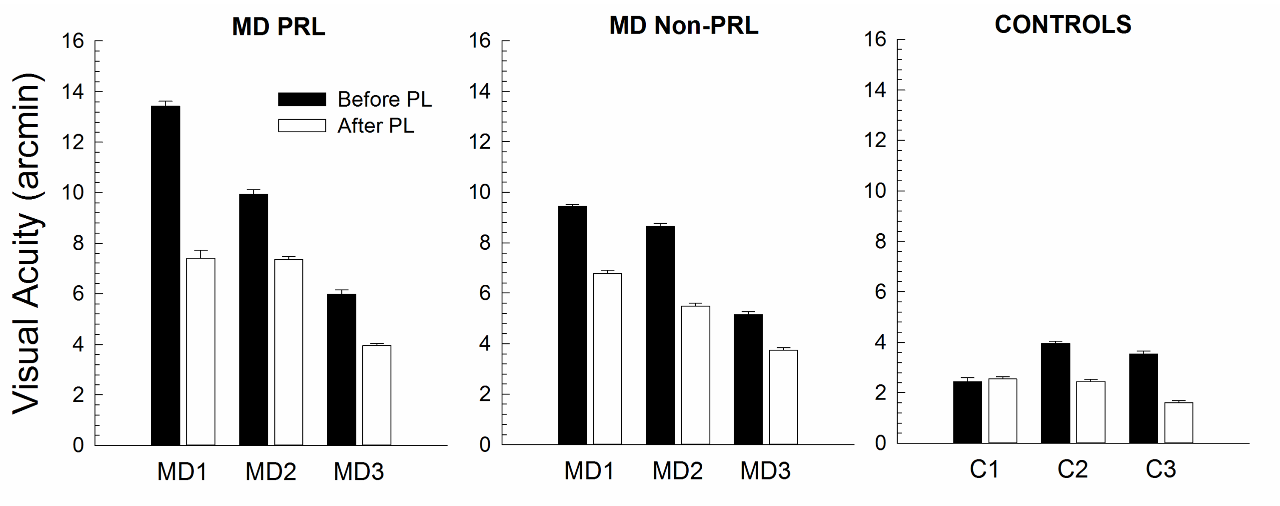

MD1
MD2
MD3
CONTROLS
Before PL
After PL
Sensitivity
1000
100
10
0
1
2
3
4
5
Spatial Frequency (cpd)

Fig. 5.



MD PRL
MD Non-PRL
CONTROLS
Visual Acuity (arcmin)
Before PL
After PL
16
14
12
10
8
6
4
2
0
MD1
MD2
MD3
C1
C2
C3

Fig. 6.

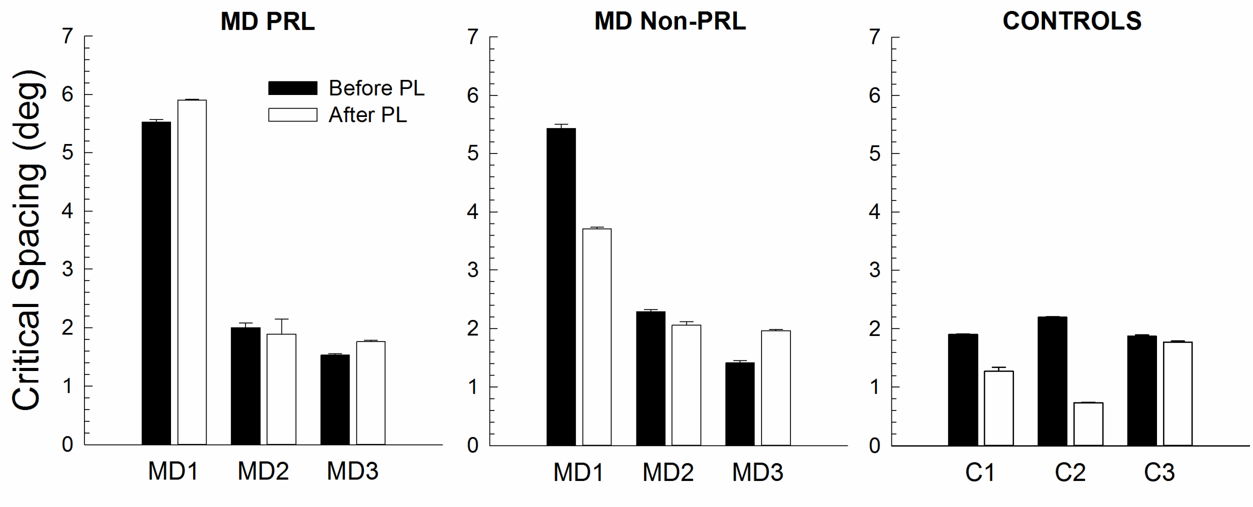

MD PRL
MD Non-PRL
CONTROLS
Critical Spacing (deg)
Before PL
After PL
0
1
2
3
4
5
6
7
MD1
MD2
MD3
C1
C2
C3

Fig. 7.

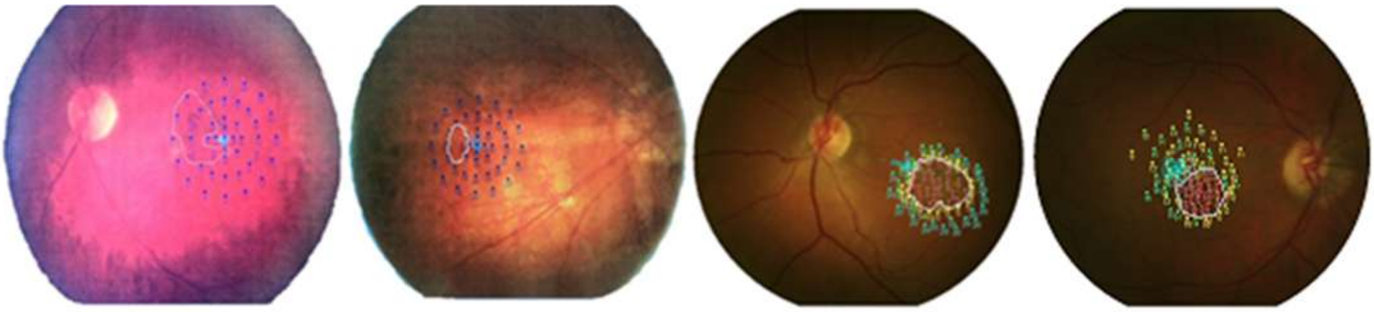


Fig. 8.

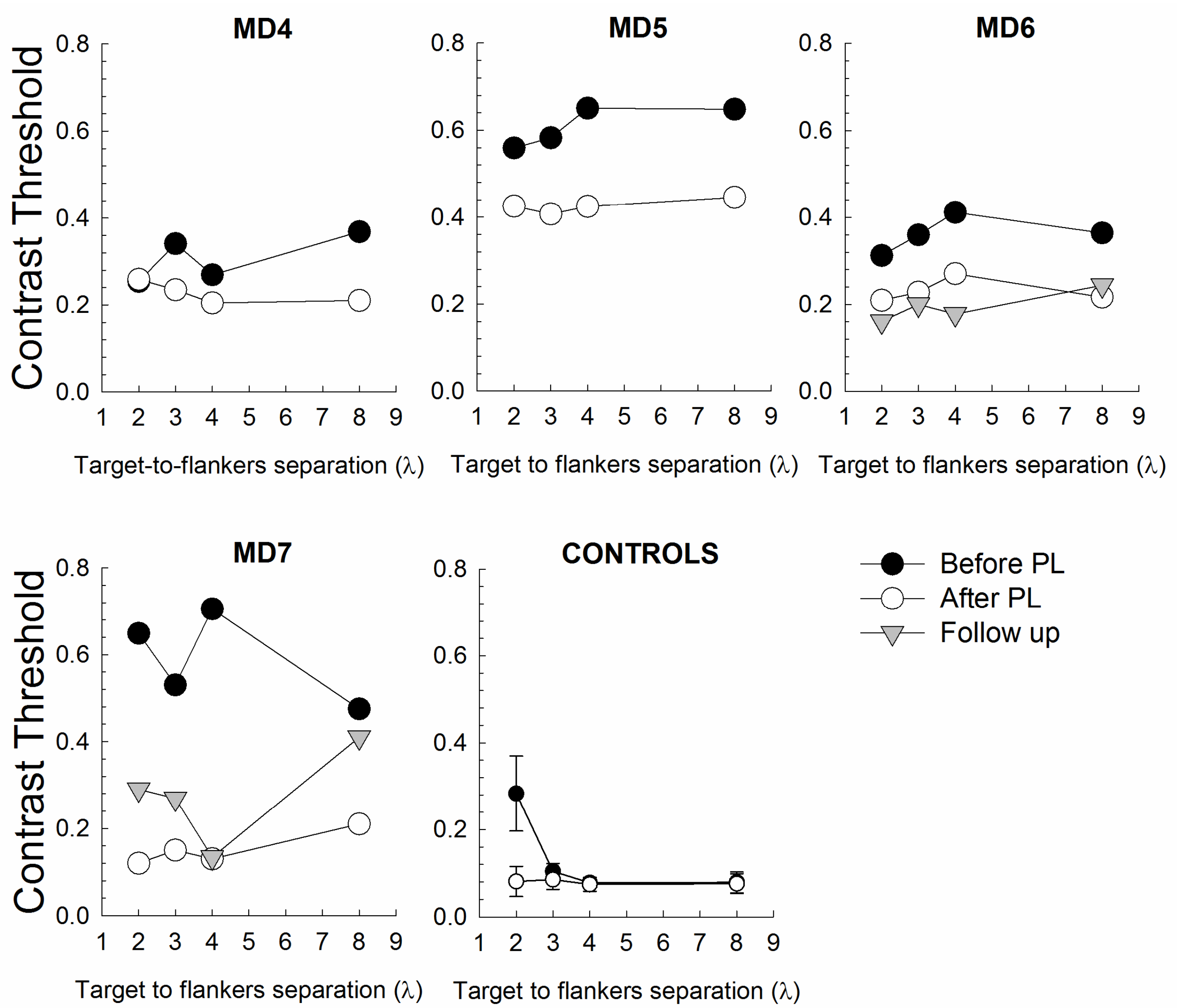
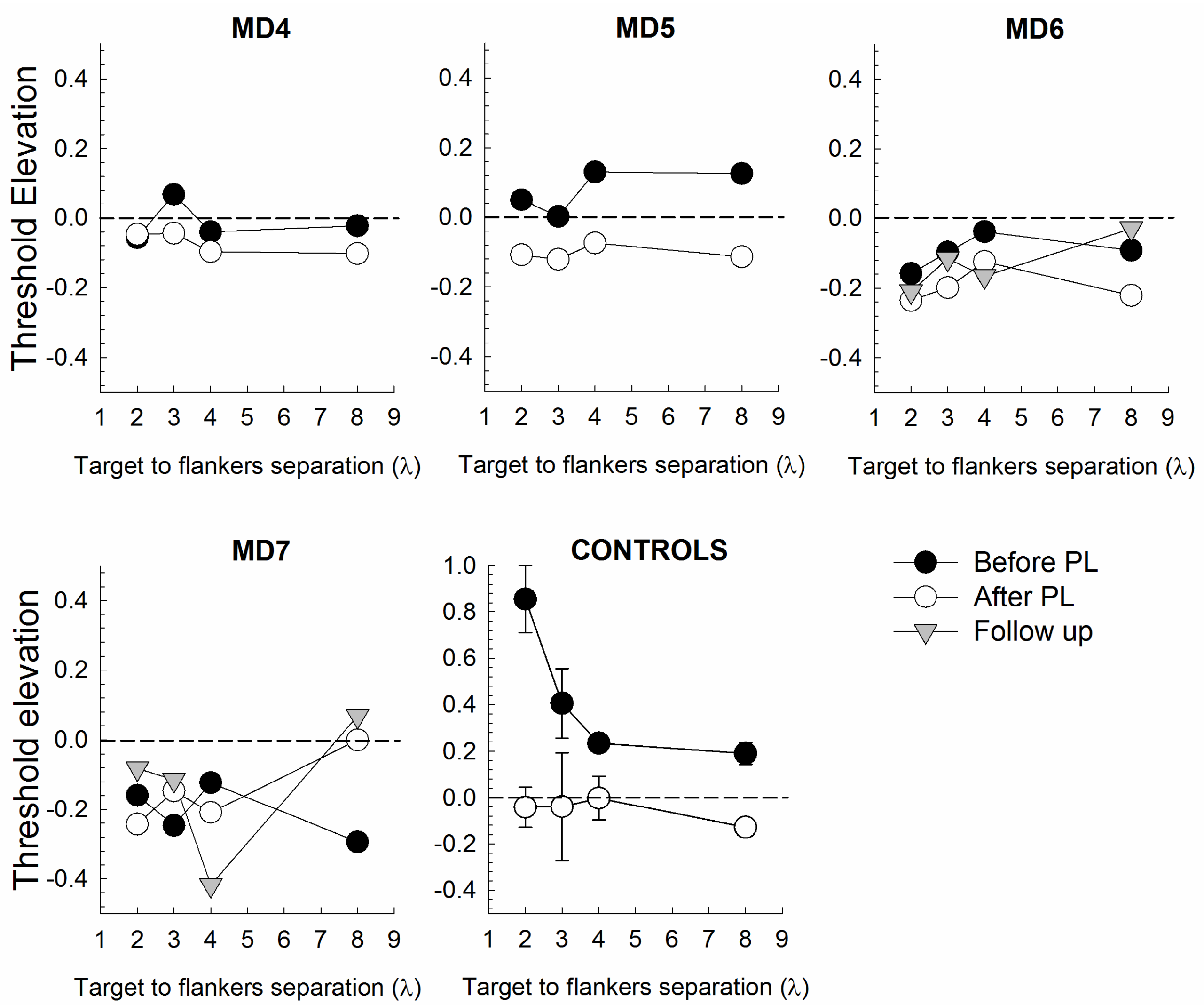
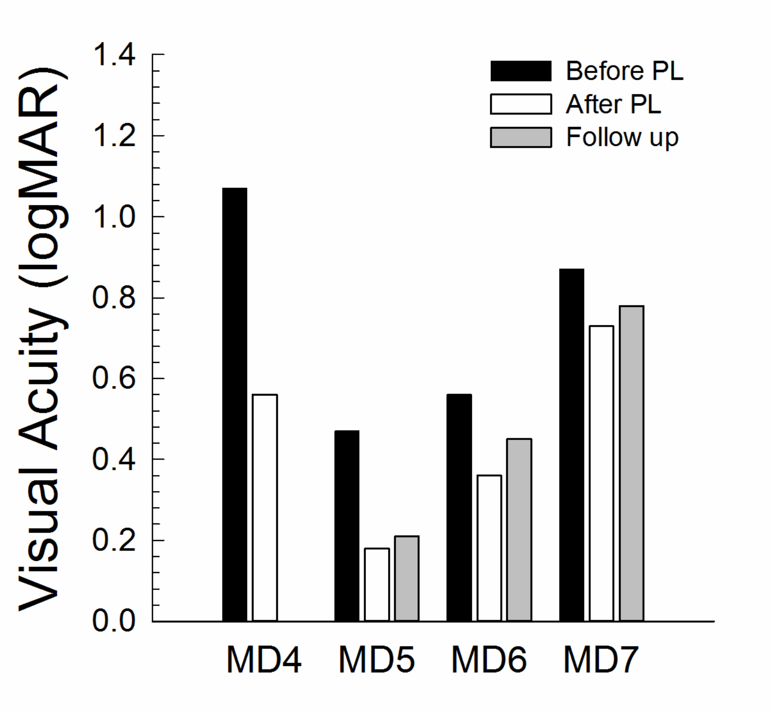

MD4
MD5
MD6
Contrast Threshold
0.8
0.6
0.4
0.2
0.0
1 2 3 4 5 6 7 8 9
Target-to-flankers separation (λ)
Target to flankers separation (λ)
Target to flankers separation (λ)
MD7
CONTROLS
Contrast Threshold
Target to flankers separation (λ)
Target to flankers separation (λ)
Before PL
After PL
Follow up

Fig. 9.



MD4
MD5
MD6
Threshold Elevation
0.4
0.2
0.0
-0.2
-0.4
1 2 3 4 5 6 7 8 9
Target to flankers separation (λ)
MD7
Threshold elevation
CONTROLS
1.0
0.8
0.6
Before PL
After PL
Follow up

Fig. 10.



Visual Acuity (logMAR)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Before PL
After PL
Follow up
MD4
MD5
MD6
MD7

Fig. 11.

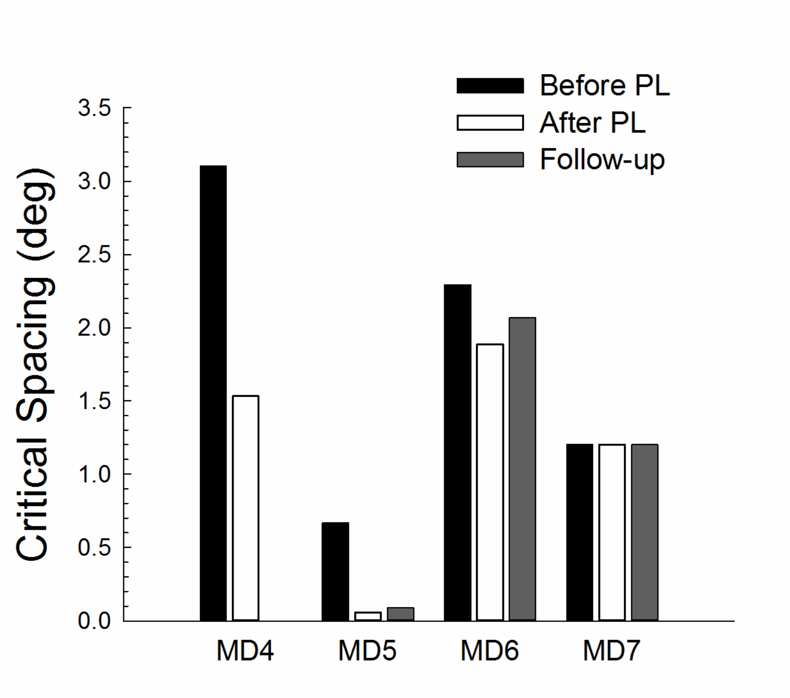
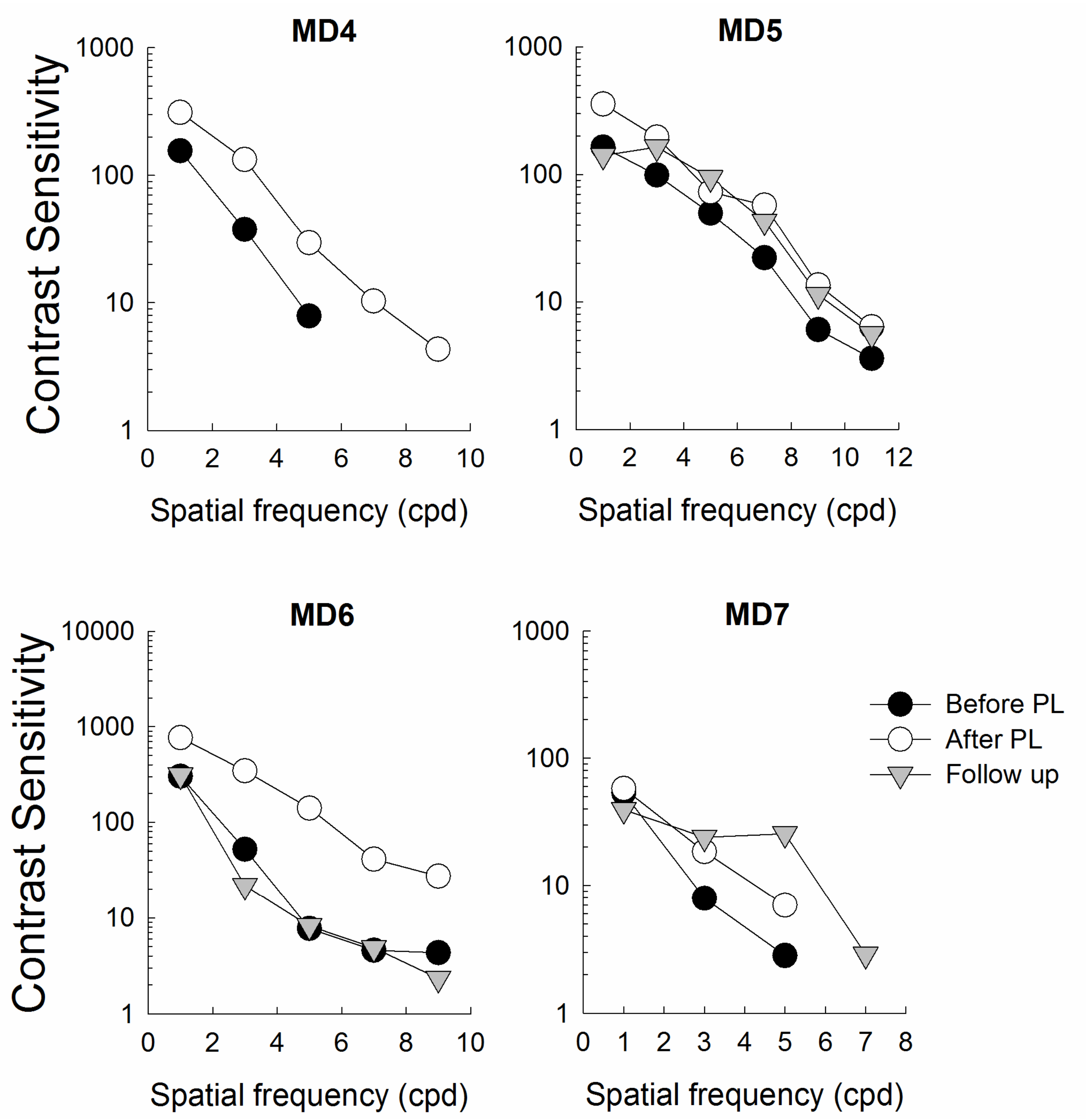

Before PL
After PL
Follow-up
Critical Spacing (deg)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
MD4
MD5
MD6
MD7

Fig. 12.



MD4
MD5
MD6
MD7
Contrast Sensitivity
Contrast Sensitivity
Spatial frequency (cpd)
Spatial frequency (cpd)
Spatial frequency (cpd)
Spatial frequency (cpd)
Before PL
After PL
Follow up

Fig. 13.